REMARKS

Claims 1, 4, 7, 8 and 54-63 are pending. The claims are not amended, and the listing of the claims is presented for the Examiner's convenience.

The amendments to page 76, line 9 of the specification to correct a typographical error are supported, for example, by page 76, line 6 of the specification.

I. The 35 U.S.C. § 112, First Paragraph "New Matter" Rejection of the Claims

The Examiner rejected claims 54-63 under 35 U.S.C. § 112, first paragraph, alleging that those claims fail to comply with the written description requirement. The Examiner alleges that those claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that the claimed "neutral" or "positively charged amino acid residue" is not supported in the specification as filed. The Examiner further alleges that the "open" amino acid residues at positions 7, 9 or 23 are not supported in the as-filed specification. This rejection is respectfully traversed.

With respect to the phrases "neutral" or "positively charged amino acid residue", Applicant respectfully directs the Examiner's attention to the specification, for example, to page 71, lines 13-22, where Applicant explains the concept of substituting a neutral or positively-charged amino acid residue for at least one of the negatively-charged residues Asp 7, Asp 23 or Glu 9 of an Fn3 molecule so as to improve the stability of the molecule:

> "The spatial proximity of Asp 7 and 23, and Glu 9 explains the unfavorable electrostatic interactions in FNfn10 identified in this study. At low pH where these residues are protonated and neutral, the repulsive interactions are expected to be mostly relieved. Thus, it should be possible to improve the stability of FNfn10 at neutral pH, by removing the electrostatic repulsion between these three residues. Because Asp 7 is centrally located among the three residues, it was decided to mutate Asp 7. Two mutants, D7N and D7K were prepared. The former neutralizes the negative charge with a residue of virtually identical size. The latter places a positive charge at residue 7 and increases the size of the side chain."

The originally-filed disclosure provides sufficient support as long as it would have reasonably conveyed to one having ordinary skill in the art that an Applicant had possession of the concept of what is now claimed. In re Anderson, 176 U.S.P.Q. 331, 336 (C.C.P.A. 1973). Applicant respectfully submits that the originally-filed disclosure reasonably conveys to one having ordinary skill in the art that an Applicant had possession of the concept of what is now claimed, *i.e.*, the concept of substituting a neutral or positively charged amino acid residue for at least one of the negatively-charged residues Asp 7, Asp 23 or Glu 9 of an Fn3 molecule so as to improve the stability of the molecule.

With respect to the amino acid residues at positions 7, 9 or 23 of claim 57, Applicant respectfully submits that the specification as-filed, *e.g.*, at page 76, lines 6-12, provides adequate support for the pending claim:

> "The carboxyl triad (Asp 7 and 23, and Glu 9) is highly conserved in FNfn10 from nine different organisms that were available in the protein sequence databank at National Center for Biotechnology Information (www.ncbi.nlm.nih.gov). In these FNfn10 sequences, Asp 7 is conserved except one case where it is replaced with Asn, and Glu 9 is completely conserved. The position 23 is either Asp or Glu, preserving the negative charge. As was discovered in this study, the interactions among these residues are destabilizing."

Applicant respectfully submits that it is clear, *e.g.*, from page 76, lines 6-12, that the originally-filed disclosure reasonably conveys to one having ordinary skill in the art that an Applicant had possession of the concept of what is now claimed, *i.e.*, the concept of substituting an amino acid residue for at least one of amino acid residues 7, 9 or 23 of an FNfn10 molecule so as to improve the stability of the molecule.

Thus, Applicant respectfully requests that the Examiner withdraw the "new matter" rejection of claims 54-63 as the originally-filed disclosure provides sufficient support for those claims, *e.g.*, because it reasonably conveys to one having ordinary skill in the art that an Applicant had possession of the concepts of what is now claimed.

II. The 35 U.S.C. § 112, First Paragraph "Written Description" Rejection of the Claims

The Examiner rejected claims 1, 8 and 54-63 under 35 U.S.C. § 112, first paragraph, alleging that those claims fail to comply with the written description requirement. The Examiner alleges that those contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Independent claim 1 recites a modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Claims 8 and 54-56 depend directly or indirectly from claim 1.

Independent claim 57 recites a modified tenth type III module of fibronectin (FNfn10) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue. Claims 58-63 depend directly or indirectly from claim 57.

Applicant asserts that the specification as originally filed provides an adequate written description of the claimed invention. Applicant may show adequate written description by demonstrating that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics that provide evidence that Applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem. v. Gen-Probe Inc.*, 323 F.3d 956, 963, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.3d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Furthermore, the written description requirement states that the Applicant must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance

also evolves between what is known and what is added by each inventive contribution. *Capon v. Eshhar v. Dudas*, 2005 U.S. App. LEXIS 16865 (Fed. Cir. 2005). Moreover, it is not necessary that every permutation within a generally operable invention be effective in order to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar v. Dudas*, 2005 U.S. App. LEXIS 16865 (Fed. Cir. 2005).

Applicant provides structural characteristics of the claimed Fn3 molecules, including the claimed FNfn10 molecules. For example, the structure of wild-type Fn3 molecules are known (*see, e.g.*, Main *et al.* 1992, of record, and page 18, line 14, through page 20, line 5 of the specification). The claimed modified Fn3 molecules have a mutation of the Fn3 structure, *i.e.*, a substitution of at least one of amino acid residues 7, 9, or 23, *e.g.*, at least one of Asp 7, Asp 23 or Glu 9, with another amino acid residue. As such, Applicant has recited specific structural modifications of the Fn3 molecules. Thus, Applicant provides the art worker with structural characteristics of the claimed modified Fn3 molecules.

Applicant also provides functional characteristics of the claimed modified Fn3 molecules, namely, that the modified Fn3 molecules comprise a mutation that is a stabilizing mutation. A stabilizing mutation is defined in the specification at page 6, lines 20-24, as "a modification or change in the amino acid sequence of the Fn3 molecule, such as a substitution of one amino acid for another, that increases the melting point of the molecule by more than 0.1°C as compared to a molecule that is identical except for the change." Applicant provides a method for determining the melting point of the molecules in Example 19, which begins at page 63 of the specification. Thus, Applicant provides the art worker with functional characteristics of the claimed modified Fn3 molecules.

To the extent that the Examiner's rejection may be made based on the allegation that the claims encompass inoperative embodiments, the Examiner is requested to note that claims are in accord with the requirements of 35 U.S.C. § 112 if one of skill in the art, guided by the specification, could avoid inoperable combinations and practice the invention without undue experimentation. The mere possibility that a claim embraces inoperable embodiments does not render it unduly broad. In addition, it is not a function of the claims to specifically exclude all

possible inoperative substances. Applicant respectfully submits that one of skill in the art, guided by the specification, could avoid inoperable combinations and practice the invention without undue experimentation.

Applicant thus respectfully asserts that sufficient detail of the identifying structural and functional characteristics of the modified Fn3 molecules have been provided or were available to one of ordinary skill in the art at the time the application was filed, and as such, Applicant was in possession of the full scope of the claimed invention at the time the application was filed.

The Examiner at page 7 of the Office Action concludes that "numerous unforeseen forces would not lead a skilled artisan to the huge scope of the claimed genus drawn to any amino acid and/or positive or neutral residues." Claims 1 and 57 recite that the modified Fn3 molecules comprise a substitution of at least one of amino acid residues 7, 9 or 23, *e.g.*, Asp 7, Asp 23 or Glu 9, with another amino acid residue. Applicant submits that the art worker is well apprised of potential amino acid residues to consider for substitution, including positive and neutral amino acids, and lists of those amino acids can be found in numerous sources. For example, Tables 3 and 4 of Chapter 2400 of the MPEP provide the art worker with some amino acids (Table 3) and modified or unusual amino acids (Table 4) that could be considered for substitution for at least one of amino acid residues 7, 9 or 23 of the Fn3 molecule. In addition, the CRC Handbook of Chemistry and Physics also provides the art worker with information regarding specific properties of common amino acids (CRC Handbook of Chemistry and Physics; 76th Edition 1995-1996; CRC Press, Inc., Boca Raton, c1995, page 7-1; a copy of provided herewith). In particular, Applicant asserts that once Applicant discovered that amino acid residues 7, 9 or 23 of the Fn3 molecule were amino acids that contributed to unfavorable intra-molecular electrostatic interactions, one of ordinary skill in the art would know or be able to determine which amino acid residues could be substituted to enhance the stability of the Fn3. For example, Applicant submits that one of skill in the art would know that since both Asp and Glu have negative charges, the introduction of an amino acid that has either a neutral or positive charge would likely reduce or remove the unfavorable electrostatic interaction from amino acid residues 7, 9

and/or 23 and would thus provide a likely candidate for substitution. Applicant has provided the art worker evidence of this as a substitution of Asp 7 with a neutral (*e.g.*, Asn) or positively-charged (*e.g.*, Lys) amino acid reduces the unfavorable interactions (page 75, lines 6-8 of the specification). And even if, for the sake of argument, the art worker lacked guidance as to which amino acid residue to select for substitution, the scope of the claims is described functionally as the substitution is recited to stabilize the molecule. As such, the art worker would need only to test the substitution(s) at the recited position(s) to determine whether the substitution stabilized the molecule using, *e.g.*, the assay described in Example 19. Applicant submits that such testing would not be undue.

Thus, Applicant has provided structural characteristics of the claimed modified Fn3 molecules as the structure of wild-type Fn3 molecules were known to the art worker at the time the application was filed. Applicant has recited specific structural modifications to the known Fn3 molecule, *i.e.*, the modified Fn3 molecule has a substitution of at least one of amino acid residues 7, 9 or 23, *e.g.*, Asp 7, Asp 23 or Glu 9. Applicant has also recited functional characteristics of the claimed modified Fn3 molecules, namely, that the modified Fn3 molecules comprise a stabilizing mutation, which mutation is functionally described in the specification together with an assay to measure the functional characteristic. Applicant has further provided examples of stabilizing mutations of the recited amino acids. Thus, it is respectfully asserted that Applicant has provided adequate written description of the claimed modified Fn3 molecules as Applicant has disclosed in sufficient detail the relevant identifying structural and functional characteristics that provide evidence that the Applicant was in possession of the full scope of the claimed invention at the time the application was filed. Thus, Applicant submits that the claims satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

In view of the above, Applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph.

III. The 35 U.S.C. § 103(a) Rejection of the Claims

The Examiner rejected claims 1, 4, 7-8 and 54-63 under 35 U.S.C. § 103(a), alleging that those claims are unpatentable over Koide (WO 98/56915; hereinafter Koide) or Lipovsek *et al.* (U.S. Patent No. 6,818,418; hereinafter Lipovsek) in view of Spector *et al.* (*Biochemistry, 39,* 872-879 (2000); hereinafter Spector). This rejection is respectfully traversed.

Independent claims 1 and 57 are described hereinabove. Claims 4, 7-78, and 54-56 depend directly or indirectly from claim 1, and claims 58-63 depend directly or indirectly from claim 57.

Koide relates to Fn3 polypeptide monobodies. Only mutant fibronectin molecules with reduced stability relative to wild type fibronectin are disclosed in Koide (*e.g.*, Figure 16 and Example XVII).

Lipovsek relates to antibody mimics that are based on the structure of an Fn3 (column 7, lines 63-65). Lipovsek states that for the human ^{10}Fn3 sequence, at a minimum, amino acids 1-9, 44-50, 61-54, 82-94 (edges of beta sheets); 19, 21, 30-46 (even), 79-65 (odd) (solvent-accessible faces of both beta sheets); 21-31, 51-56, 76-88 (CDR-like solvent-accessible loops); and 14-16 and 36-45 (other solvent-accessible loops and beta turns) may be randomized to evolve new or improved compound-binding proteins (column 9, lines 24-31).

Spector relates to the electrostatic contributions that charged and polar side chains make on the overall stability of a 41-residue protein (first sentence of the Abstract), a protein that is based on the peripheral subunit-binding domain, derived from the dihydrolipoamide acetyltransferase component of the pyruvate dehydrogenase multienzyme complex from *Bacillus stearothermophilus* (page 873, first column, second full paragraph).

A rejection of obviousness under 35 U.S.C. § 103 requires that the Examiner establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner has the burden to establish three basic elements. First, the Examiner must establish that there is some suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention. Second, the Examiner must establish that there is a

reasonable expectation of success. Finally, the Examiner must establish that the prior art documents teach or suggests all the claim limitations. M.P.E.P. 2143. Applicant respectfully submits that the Examiner has not demonstrated that the claims are *prima facie* obvious in view of the cited documents, for example, because the Examiner has not established that the cited documents teach or suggests all the claim limitations. And, even if, for the sake or argument, the cited documents teach or suggests all the claim limitations, Applicant respectfully submits that the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention.

At page 11 of the Office Action, the Examiner states neither Koide nor Lipovsek teaches that the regions of Fn3 containing amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction, as claimed. Applicant respectfully submits that Spector does not remedy the deficiencies of Koide and Lipovsek because Spector does not teach or suggest that the regions of Fn3 containing amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction. Spector is related to the peripheral subunit-binding domain, derived from the dihydrolipoamide acetyltransferase component of the pyruvate dehydrogenase multienzyme complex from *Bacillus stearothermophilus*, not to Fn3. Thus, Applicant submits that the Examiner has not established that the cited documents teach or suggests all the claim limitations, *e.g.*, a modified Fn3 or FNfn10 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3 or FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 (e.g., Asp 7, Asp 23 or Glu 9) with another amino acid residue.

At page 12 of the Office Action, the Examiner alleges that it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine whether the amino acids in the 1-9 or 21-31 regions of Fn3 of Koide or Lipovsek are involved in an unfavorable electrostatic interaction as taught by Spector (underline added). However, as stated in MPEP 2145(X)(B), 'obvious to try' is not the standard under § 103. Specifically, trying each of numerous possible choices until one possibly arrived at a successful result, where the prior art

gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, is an improper 'obvious to try' standard. Applicant respectfully submits that the Examiner is improperly relying on an "obvious to try" standard by suggesting that the art worker could have tried each of numerous possible choices, *i.e.*, the listing of amino acids, until the art worker possibly arrived at a successful result.

Thus, Applicant respectfully submits that the cited documents, neither alone nor in combination, teach a modified Fn3 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Nor do the cited documents, either alone or in combination, teach a FNfn10 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue. Thus, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103(a).

IV. Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is respectfully requested.

The Examiner is invited to telephone Applicant's attorney to facilitate prosecution of this application. If necessary, please charge any additional required fees or credit any overpayments to Deposit Account No. 503503.

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 2nd day of May 2006.

Lynda Mau _____
Name Signature

PROPERTIES OF COMMON AMINO ACIDS

This table gives selected properties of 20 α-amino acids commonly found in proteins. The structures of these amino acids are given in a separate table. The compounds are listed in alphabetical order by the three-letter symbols. Dissociation constants refer to aqueous solutions at 25° C.

M_r — Molecular weight
T_m — Melting point
pK_a — Negative of the logarithm of the dissociation constant for the α-COOH group
pK_b — Negative of the logarithm of the dissociation constant for the α-NH_3^+ group
pK_x — Negative of the logarithm of the dissociation constant for any other group present in the molecule
pI — pH at the isoelectronic point
S — Solubility in water at 25° C in units of grams per kilogram of water

Symbol	Name	Mol. form.	M_r	T_m/°C	pK_a	pK_b	pK_x	pI	S
Ala	Alanine	$C_3H_7NO_2$	89.09	297	2.34	9.69		6.00	167
Arg	Arginine	$C_6H_{14}N_4O_2$	174.20	238	2.17	9.04	12.48	10.76	181
Asn	Asparagine	$C_4H_8N_2O_3$	132.12	236	2.02	8.80		5.41	25
Asp	Aspartic acid	$C_4H_7NO_4$	133.10	270	1.88	9.60	3.65	2.77	5
Cys	Cysteine	$C_3H_7NO_2S$	121.16	178	1.96	10.28	8.18	5.07	
Gln	Glutamine	$C_5H_{10}N_2O_3$	146.15	185	2.17	9.13		5.65	42
Glu	Glutamic acid	$C_5H_9NO_4$	147.13	249	2.19	9.67	4.25	3.22	
Gly	Glycine	$C_2H_5NO_2$	75.07	290	2.34	9.60		5.97	251
His	Histidine	$C_6H_9N_3O_2$	155.16	277	1.82	9.17	6.00	7.59	43
Ile	Isoleucine	$C_6H_{13}NO_2$	131.17	284	2.36	9.60		6.02	34
Leu	Leucine	$C_6H_{13}NO_2$	131.17	337	2.36	9.60		5.98	23
Lys	Lysine	$C_6H_{14}N_2O_2$	146.19	224—225	2.18	8.95	10.53	9.74	6
Met	Methionine	$C_5H_{11}NO_2S$	149.21	283	2.28	9.21		5.74	56
Phe	Phenylalanine	$C_9H_{11}NO_2$	165.19	284	1.83	9.13		5.48	29
Pro	Proline	$C_5H_9NO_2$	115.13	222	1.99	10.60		6.30	1622
Ser	Serine	$C_3H_7NO_3$	105.09	228	2.21	9.15		5.68	422
Thr	Threonine	$C_4H_9NO_3$	119.12	253	2.09	9.10		5.60	97
Trp	Tryptophan	$C_{11}H_{12}N_2O_2$	204.23	282	2.83	9.39		5.89	12
Tyr	Tyrosine	$C_9H_{11}NO_3$	181.19	344	2.20	9.11	10.07	5.66	0.5
Val	Valine	$C_5H_{11}NO_2$	117.15	292-295	2.32	9.62		5.96	58

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